

REMARKS / ARGUMENTS

Claim 3 was rejected under 35 USC 112, second paragraph. Applicants request reconsideration and withdrawal of this rejection in view of the following discussion.

The Examiner's attention is directed to the last paragraph on page 12 of the specification which describes appropriate concentrations of imatinib for synergy and indicates that the synergy does not appear to be dose dependent. Based on this information, one of ordinary skill in the art would have no difficulty determining the metes and bounds of claim 3. Therefore, claim 3 conforms with the requirements of 35 USC 112, second paragraph. Accordingly, withdrawal of the rejection is requested.

Claims 1-7 and 10 were rejected under 35 USC 102(b) as being anticipated by Virchis et al. Applicants request reconsideration and withdrawal of this rejection for the reasons that follow.

The present claims are directed to a combination of a nitrogen mustard analog, including chlorambucil, with imatinib for the treatment of CLL. According to example 1 of the present application, imatinib synergistically sensitized CLL-lymphocytes isolated from patients to treatment with chlorambucil, which induces cell death.

In contrast, Virchis et al, although reporting experiments using chlorambucil and imatinib conducted on lymphocytes derived from CLL patients, does not suggest that the combination should be used to treat CLL, and, indeed, one of ordinary skill would reach the opposite conclusion from the reference. The last sentence of the reference discloses that the activation of c-Abl protein tyrosine kinase couples DNA damage induction by chlorambucil to p53 upregulation and subsequent apoptosis in B-CLL cell lines. Because imatinib is a specific inhibitor of c-Abl kinase, the reference discloses that it counteracts the effect of chlorambucil. Thus, the reference does not teach any utility for the combination and indeed teaches against the claimed combination which is used to treat patients with CLL. Therefore, the present combinations are novel over Virchis et al.

Claims 1-7 and 10 were rejected under 35 USC 103(a) over Kimby et al and Tallman in view of Esteve et al. Applicants request reconsideration and withdrawal of this rejection for the reasons that follow.

Kimby et al is relied on as disclosing that chlorambucil is used to the treatment of B-CLL. Tallman discloses that imatinib is used to treat a different type of leukemia, CML. Esteve et al is relied on as disclosing that CML and CLL can co-exist in the same patient.

Virchis et al is not used as a reference in this rejection. However, its disclosure would lead one of ordinary skill to expect that imatinib would have an antagonistic effect on treatment with chlorambucil. Therefore, the prior art as a whole, teaches against the present combination. The Examiner has not pointed out any disclosure in Kimby et al, Tallman or Esteve et al which overcomes the clear teaching away of Virchis et al. Therefore, Applicants assert that the present combination is not *prima facie* obvious over the art as a whole.

In addition, Example 1 demonstrates that the addition of imatinib to chlorambucil therapy produces a synergistic effect. This synergy could not have been predicted from the references and is clearly unexpected based on the disclosure of Virchis et al. Therefore, the present combinations are patentable over the references.

Applicants request withdrawal of the rejection of claims 1-7 and 10 under 35 USC 103(a) for the reasons discussed above.

Claim 11 is rejected under 35 USC 103(a) over Kimby et al and Tallman in view of Esteve et al and further in view of MacLeod. Applicants request reconsideration and withdrawal of this rejection for the reasons that are discussed above with respect to the rejection of claims 1-7 and 10.

Claim 11 is rejected under 35 USC 103(a) over Virchis et al in view of MacLeod. Applicants request reconsideration and withdrawal of this rejection for the reasons that are discussed above with respect to the rejection of claims 1-7 and 10.

Entry of this amendment and reconsideration and allowance of the claims are respectfully requested.

Respectfully submitted,

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